REMARKS

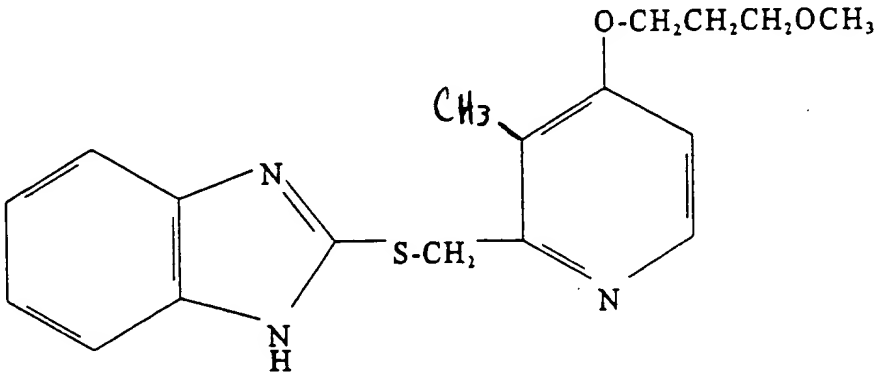
Claims 18 and 19 are active in the application. An Abstract of the Disclosure is attached to this response on a separate sheet as requested on page 2, first paragraph of the Official Action.

Also filed with this response is true and correct copy of the specification of this application as originally filed as Serial No. 07/119,386 on November 10, 1987. This responds to the examiner's request on page 2, third paragraph, of the Official Action. I hereby certify that this is a true and correct copy of the first filed text of this application and that no new matter is presented. A clean copy of claim 18 showing the formula is also attached.

The claims of the present application are rejected on the basis of prior art as well as alleged double patenting. Counsel wishes to defer the issues of double patenting and provisional double patenting until such time as the art-based issues have been resolved.

Claims 18 and 19 stand rejected as allegedly being obvious over European patent application 074,341 (page 20, Example 27) by itself or in view of published European application 198,208.

The claims of this application are directed to compounds having the structure



Claimed Compound

It is this compound that is converted to the corresponding sulfinyl compound that is the subject of great-grandparent application, now U.S. Patent No. 5,045,552.

The only difference in structure is that the claim compounds are thios whereas the patent compounds sulfinyls. Indeed, it is the structure of the presently claimed compound that affords the desired sulfinyl compounds and is, in fact, the last step in the synthesis process for making such compounds. Note that there is only one structural change in the compound made prior to the finished product. Thus, it is clear that the claim compounds serve as valuable and useful intermediates to produce the patented compounds. From the record of great grandparent application and the present application as well it is clear that the patented compounds have unexpected properties compared to related compounds in the prior art. These unexpected properties in part flow from the specific structure of the compounds of the present application and, in particular, the substituent on the four position of the pyridine ring which remains unchanged between the claimed compounds of the present application and the patented compounds.

The examiner's attention is directed to *In re Magerlein*, 202 U.S.P.Q. 473 at 478 (CCPA 1979) where the court stated:

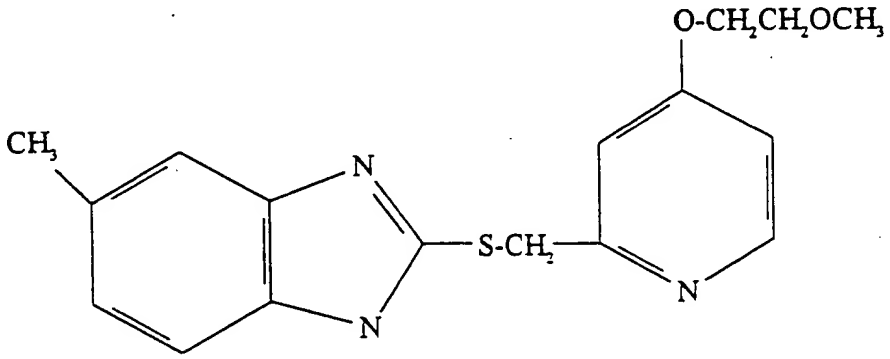
> "...evidence of an unexpectedly superior activity or property of an end product may, under appropriate circumstances, be considered in the determination of the nonobviousness of the claimed intermediate."

And thereafter concluded

> "...we are persuaded that the capacity of an intermediate to contribute to an end product that feature which causes the end product to possess an activity or property that is unexpectedly superior to that of a prior art end product is a 'property' that inures to the benefit of the intermediate and that can be considered as part of the 'subject matter as a whole' in determining the nonobviousness of the intermediate."

Based on the above legal reasoning, it is respectfully submitted that the claims of the present application defined inventive subject matter -- the compounds of the present application include features which cause the end product to possess an activity or property that is unexpectedly superior to that of the prior art end products. This has been demonstrated by the issuance of U.S. Patent No. 5,045,552 and as explained above.

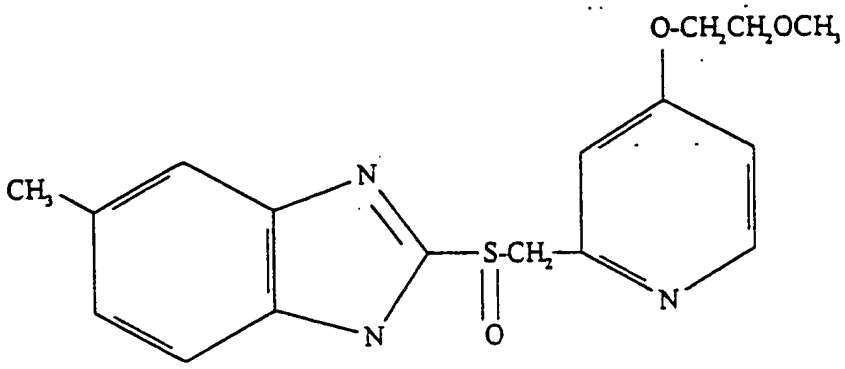
A compound of EP '314 considered by the examiner as representative of that disclosure is as follows:



EP 074,341 Hassle

In addition to a methyl group in the five position of the benzimidazol ring, the substituent at the four position of the pyridine ring is methoxyethoxy, an issue directly pertinent to and dealt with during the examination of the application that matured in the U.S. Patent No. 5,045,552.

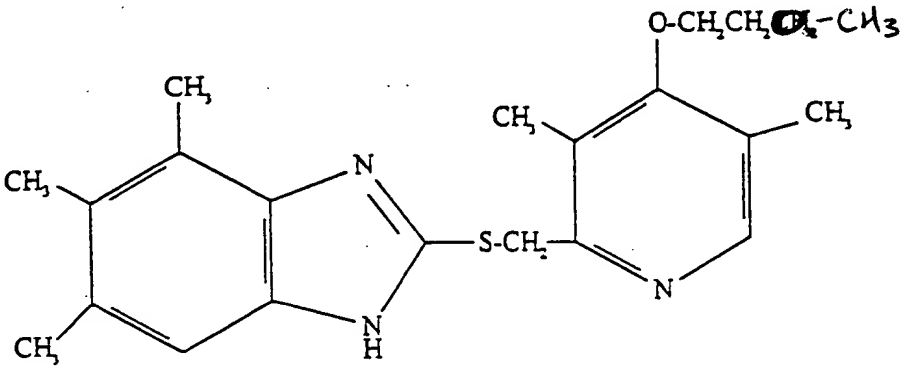
Also cited against claims 18 and 19 is U.S. Patent No. 4,508,905 to Jurggren et al, the compound of particular interest having the following structure:



U.S. 4,508,905 Jurggren et al

Note that the linking group is a sulfinyl whereas the substituent on the four position of the pyridine ring is again methoxyethoxy, thus, Jurggren's compounds do not possess the relevant structure to lead to the patent compounds as do the compounds of the present application.

Similarly, British patent specification 2,134,523 to Hassle was cited and applied to claims 18 and 19 of the present application. The examiner pointing to page 16, line 9, from the bottom of that disclosure for what is regarded to be a representative compound. It has the following structure:



GB 2,134,523 Hassle

This particular compound contains five methyl groups, one each at positions 5, 6 and 7 of the benzimidazol ring, two methyl groups on the 3 and 5 positions of the pyridine ring and, as with Jurggren et al discussed above, a methoxyethoxy group is at the 4 position of the pyridine ring. The examiner's only citation pertaining to the substituents on the 4 position of the pyridine ring is published European application 0198208, specifically at column 2, lines 23 and 24. Applicants have already dealt with this issue during the examination of the great-grandparent application which resulted in the issuance of a U.S. patent. Thus, the determination has already been made that in these compounds methoxypropoxy provides properties superior to related compounds. Moreover, there is no disclosure or suggestion in EP '208 of any significant differences in the substituents on the 4 position of pyridine ring. Applicants, of course, have determined otherwise.

For these reasons, it is respectfully submitted that the claims of this application define inventive subject matter.

Presentation of Additional Information and Data

Applicants have determined in collateral studies that the compounds of the present application possess antibiotic properties superior to those of the structurally related compounds. This subject matter is now before the USPTO in application Serial No. 08/379,214, filed January 27, 1995, and pending in art unit 1206. Attached are relevant portions of the specification of that application showing comparison of various compounds, many of which are pertinent to the prior art of the present application, with the compound of the present application, identified as (II). Please see pages 13-17 reporting the results of testing of compound II (see Table 1, page 16) with related compounds. The superior antibiotic activities of these compounds will be apparent.

As this information is already contained in a pending U.S. application counsel believes that it does not need to be separately verified. Counsel will provide a suitable declaration if the examiner so requests.

For the above reasons, it is respectfully submitted that the claims of this application define inventive subject matter. Reconsideration of this application and favorable action are solicited.

Respectfully submitted,

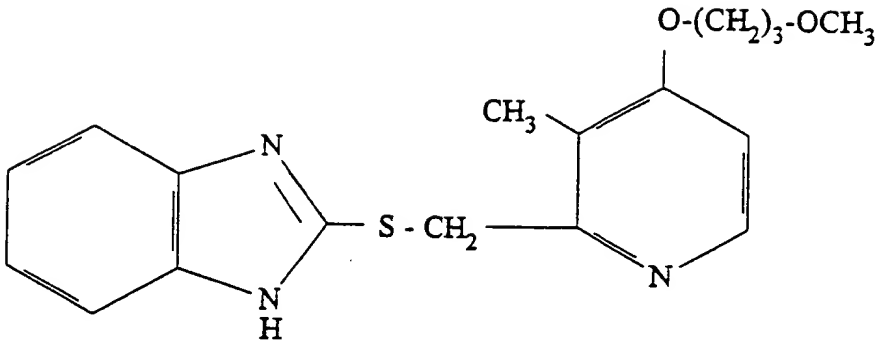
NIXON & VANDERHYE P.C.

By: _____

Arthur R. Crawford
Reg. No. 25,327

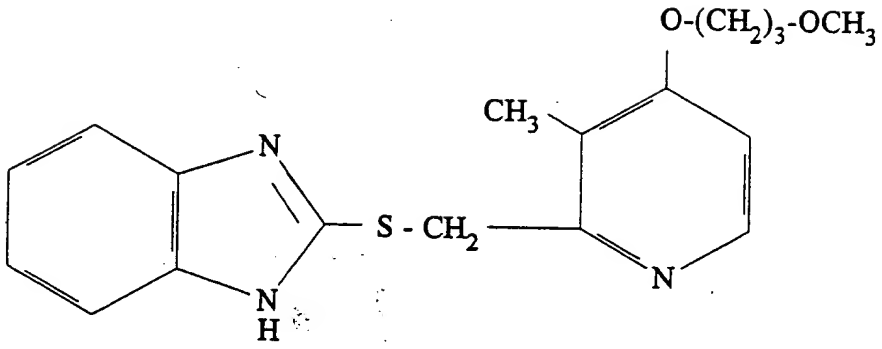
ARC:pc
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

--18. A compound represented by the formula:



or a pharmaceutically acceptable salt thereof.

--18. A compound represented by the formula:



or a pharmaceutically acceptable salt thereof.

(I)

molecular formula : $C_{18}H_{20}N_3O_3S$

molecular weight : 358.44

property : white crystaline

The physical property of 2-[(4-(3-Methoxypropoxy)-3-methylpyridine-2-yl)-methylthio]-1H-benzimidazole (II)

molecular formula : $C_{18}H_{20}N_3O_2S$

molecular weight : 342.44

property : pale yellow crystaline

Pharmacological test

Standard strains and clinical isolates of C. pylori derived from the mucous membrane of the stomach were used and determined in vitro according to the agar dilution method determined by Nihon Kagaku Ryoho Gakkai (English name: Japan Society of Chemotherapy).

Sodium salt of 2-[(4-(3-Methoxypropoxy)-3-methylpyridine-2-yl)-methylsulfinyl]-1H-benzimidazole (I) was dissolved in a sterilized water. 2-[(4-(3-Methoxypropoxy)-3-methylpyridine-2-yl)-methylthio]-1H-benzimidazole (II) and, as controls, omeprazole, 5-Methoxy-2-[(4-methoxy-3, 5-dimethyl-2-pyridinyl)methylthio]-1H-benzimidazole and 2-[(3-Methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl)methylthio]-1H-benzimidazole were dissolved

separately in a 1% dimethylsulfoxide solution. As an antibiotic substance control, roxithromycin as macrolides, ampicillin as penicillins, ofloxacin as newquinolones were dissolved in a buffer solution of acetic acid having a pH of 5.0, a sterilized water and an 1N aqueous solution of NaOH, respectively. Test plates were prepared by adding 7% horse blood to Brucella agar named by BBL Microbiology Systems (tradename), being available from Bector Dickson and Company. The incubation was conducted at 37°C at pH of 7.0 for 3 days under the microaerophilic condition using Canpipack (tradename) being available from Bector Dickson and Company. MIC was determined in unit of microgram per ml. Test results are shown in Table 1. NCTC11637 and NCTC11916 are standard stains. strains The other references indicate clinical isolates.

The test result is shown in terms of the antibiotic activity (MIC) in unit of microgram/ml. obtained in vitro against C. pylori. The tested compounds are (I) sodium salt of 2-[{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole, (II) 2-[{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole, (III) 5-Methoxy-2-[{(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl}sulfinyl]-1H-benzimidazole

2nd close

(omeprazole), (IV) 5-Methoxy-2-{(4-methoxy3,5-dimethyl-2-pyridinyl)methylthio}-1H-benzimidazole, (V) 2-[{3-Methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl}methylthio]-1H-benzimidazole, (VI) roxithromycin (RXM), (VII) ampicillin (ABPC), (VIII) ofloxacin (OFLX).

Table 1

Tested strain	Compunent							
	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)	(VIII)
NCTC11637	3.13	0.8	50	25	25	0.4	0.4	0.8
NCTC11916	3.13	0.2	25	12.5	12.5	0.1	0.05	0.8
EI-2	3.13	0.4	25	25	25	0.2	0.4	0.8
EI-5	3.13	0.2	50	25	12.5	0.2	0.4	0.8
EI-36	6.25	0.4	25	12.5	12.5	0.2	0.2	0.8
EI-46	3.13	0.4	25	12.5	12.5	>100	0.05	3.13
EI-391	3.13	1.56	50	25	12.5	50	0.1	25
EI-393	3.13	1.56	50	25	25	0.2	0.1	0.8
EI-397	3.13	1.56	50	25	25	0.2	0.1	0.8
EI-429	1.56	1.56	25	25	25	0.2	0.2	0.8
EI-467	1.56	1.56	50	12.5	12.5	0.2	0.05	0.4
EI-612	0.4	0.8	25	12.5	6.25	0.2	0.05	0.8
EI-925	3.13	0.4	25	12.5	12.5	0.2	0.2	0.4
EI-930	3.13	0.4	25	12.5	12.5	0.4	0.4	0.8
EI-933	3.13	0.8	25	12.5	12.5	0.1	0.05	0.4

It is noted from the test results that the compounds of the invention are superior to the known compounds such as omeprazole disclosed in JP-A 2-209809 and lansoprazole derivatives disclosed in JP-A 3-173817. The compounds of the

invention evidently provide an equivalent C. pylori eradicating activity to antibiotics. Since the compounds of the invention are not ~~of the~~ antibiotic compounds, the compounds of the invention work effectively ~~to a~~ against resistant bacteria such as clinically isolated strains shown in Table, EI-46 and EI-391. This is the reason they provide the antibiotic activity ~~to~~ against a wider variety of bacteria than antibiotic substances. They can be administered continuously for long term. They have been found, at a concentration of 100 micrograms per ml, not to inhibit other gram-positive and gram-negative bacillii from growing eyen. This shows the fact that they ~~can be~~ exhibit antibiotic activity selectively to C. pylori.

acute toxicological test

The compound (I) of the invention was administered intravenously or orally one time, with a carrier of saline, to Slc:SD rats and Slc:ICR mouse, each being 7 or 8 weeks old, in a group consisting of five males and five females, to determine LD_{50} values. Results are shown in Table 2.

Acute toxicity of the compound (I) is shown in terms of LD_{50} in unit of mg/kg.